

An inverse association of cardiovascular risk and frontal lobe glucose metabolism

B. Kuczynski, PhD
W. Jagust, MD
H.C. Chui, MD
B. Reed, PhD

Address correspondence and reprint requests to Dr. Beth Kuczynski, University of California, Helen Wills Neuroscience Institute, 118 Barker Hall MC 3190, Berkeley, CA 94720
beth.kuczynski@gmail.com

ABSTRACT

Objective: To investigate associations between vascular risk profile and cerebral glucose metabolism.

Methods: Subjects ranged from normal to having dementia (age >55 years) and underwent neuropsychological testing, MRI, and FDG PET scanning (n = 58). The Framingham Cardiovascular Risk Profile (FCRP) and its individual components were used as covariates in regression analyses with each PET scan using SPM2.

Results: Analyses revealed broad areas of the frontal lobe in which higher FCRP was associated with lower normalized glucose metabolism including the superior medial frontal, superior frontal and superior orbital frontal cortex and the ventrolateral prefrontal cortex. Significant associations were predominately found in the left hemisphere. Independent component analyses revealed interesting regions but further confirm the relevance of the integrative measure of coronary risk.

Conclusions: Although the mechanism of this association bears further investigation, this finding provides further evidence that vascular risk factors have malignant effects on the brain, particularly in the prefrontal cortex. *Neurology*® 2009;72:738-743

GLOSSARY

2D = two-dimensional; **AD** = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CIND** = cognitively impaired not demented; **CVD** = cerebrovascular disease; **FCRP** = Framingham Cardiovascular Risk Profile; **FDG** = fluorodeoxyglucose; **FWHM** = full-width, half-maximum; **MDT2** = minimal deformation template; **MMSE** = Mini-Mental State Examination; **MNI** = Montreal Neurologic Institute; **TE** = echo time; **TR** = repetition time.

Numerous findings have expanded interest in the extent and nature of the contribution of vascular disease to dementia and cognitive impairment in the elderly. These include reports that, in community-based series, dementia is commonly associated with mixed Alzheimer disease (AD) and cerebrovascular disease (CVD) pathology,¹⁻³ perhaps even more distinctly than with AD pathology alone.¹ Numerous epidemiologic analyses have reported that well-established risk factors for cardiovascular and cerebrovascular disease are also risk factors for AD, including hypertension,^{4,5} diabetes,⁶ obesity,⁷ and lifestyle and dietary factors.⁸ These findings, together with data indicating that both vascular disease and AD affect the cerebral cortex,⁹ suggest that dementia frequently results from the interplay of vascular and degenerative pathologies.

This perspective raises the question of whether traditional vascular risk factors might also be associated with brain dysfunction. Cerebral metabolism is a basic index of cortical function; cortical hypometabolism is associated with a wide variety of disorders that cause dementia and cognitive impairment.¹⁰ Its sensitivity to pathology is demonstrated, for example, in the findings that metabolic abnormalities appear in persons at risk for AD well before clinical symptoms manifest,^{11,12} and that metabolic abnormalities precede and predict cognitive abnormalities.¹³

Supplemental data at
www.neurology.org

From the Helen Wills Neuroscience Institute, University of California, Berkeley, and the Lawrence Berkeley National Laboratory (B.K., W.J.); the Department of Neurology (H.C.C.), University of Southern California, Los Angeles; and University of California, Davis, Alzheimer's Center and Northern California Veterans Affairs Health Care System (B.R.).

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The aim of this study was to investigate whether vascular risk factors are associated with cortical hypometabolism in older adults. The Framingham Cardiovascular Risk Profile score (FCRP)¹⁴ provides a convenient method of summarizing vascular risk. Previous work suggests that the frontal lobes are particularly, though not exclusively, vulnerable to the effects of vascular lesions. Both white matter hyperintensities¹⁵ and lacunar infarcts¹⁶ are associated with hypometabolism in frontal cortex, and cognitive executive dysfunction, which itself is sensitive to frontal lobe damage. Thus, we hypothesized that higher FCRP scores would be associated with diminished metabolic activity in the frontal lobe.

METHODS Subjects. Fifty-eight subjects recruited through university dementia research programs between 1999 and 2005 were evaluated under the multi-institutional “Aging Brain” study protocol. Informed consent to participate in the study was obtained in accordance with the policies of each institutional review board. The recruitment practices were intended to enrich the sample for the presence of small vessel CVD. Criteria included being above the age of 55, and between the normal to moderate dementia range for cognitive function (Clinical Dementia Rating [CDR] score¹⁷ of 0 to 1), with scores of 0 indicating normal cognitive function, 0.5 cognitively impaired not demented (CIND), and 1 demented. Persons with radiologically defined lacunar infarcts were targeted for inclusion. Exclusionary criteria included diagnosis of cortical stroke or neurologic illnesses (other than subcortical CVD or AD), Mini-Mental State Examination (MMSE) score below 15, and the use of psychoactive drugs (other than stable doses of acetylcholinesterase inhibitors or selective serotonin reuptake inhibitors). All individuals were evaluated by clinicians at the university dementia clinics using standard criteria for vascular dementia¹⁸ and AD.¹⁹

Design. We used a multiple regression approach including all subjects without regard to diagnostic grouping based on the premise that both the independent (FCRP) and dependent (voxel-wise metabolic activity) variables are distributed continuously across these elderly subjects.

Framingham Cardiovascular Risk Profile. The FCRP, derived from the medical history, is a weighted sum of the following vascular risk factors: smoking, diabetes, hypertension, cholesterol, and age.¹⁴ Briefly, the FCRP score was created by the Framingham Study as a simple coronary disease prediction algorithm, using categorical variables to predict the risk of coronary heart disease. The algorithm was created using the average risk estimates calculated for men or women based on the typical Framingham subject data: 30 to 74 years old at baseline, optimal blood pressure, total cholesterol 160 to 199 mg/dL (or low density lipoprotein 100 to 129 mg/dL), high density lipoprotein of 45 mg/dL in men or 55 mg/dL in women, no diabetes, and no smoking, as previously described by Wilson et al.¹⁴

MRI data acquisition. All MRI data for this study were acquired on a 1.5 Tesla Siemens Vision MRI system. Sequences included a double spin echo with repetition time (TR)/echo time

(TE)1/TE2 2,500/20/80 msec, 1 excitation, 3 mm slice thickness with no slice gap, and in-plane resolution 0.94×0.94 mm². The second sequence provided the T1-weighted images via a T1 coronal magnetization-prepared rapid gradient echo spin echo axial design (TR/TE = 10/4 msec; 1 excitation), 1×1 mm² in-plane resolution with contiguous 1.4-mm-thick slices.

PET data acquisition and processing. The FDG-PET data were acquired using a Siemens-CTI ECAT EXACT (model 921), 47-slice scanner in two-dimensional (2D) acquisition mode to image the [¹⁸F]fluorodeoxyglucose (FDG) radiotracer. The scanner has a resolution of approximately 6 mm full-width, half-maximum (FWHM) at center to 7.5 mm tangentially and 9.6 mm radially (at 20 cm), with an axial resolution of 5 mm at the center and 8.1 mm FWHM at R = 20. The axial field of the scanner is 16.2 cm and the sensitivity is 216 kcps/mCi/mL for a 20 cm cylinder phantom in 2D.

The injected dose for each individual was approximately 10 mCi of FDG. Post injection, the individual was seated in a room for 40 minutes. Subjects were then positioned in the scanner to enable a field of view encompassing the entire brain. Emission data were collected in 2D for 40 minutes, followed by a 20-minute transmission period using a rotating ⁶⁸Ge source consisting of three rods of about 2 mCi/rod.

All PET scans were partial volume corrected before analyses. This correction involved creating a brain mask from the high resolution T1 MRI consisting of gray and white matter. Convolution of this brain mask with the point spread function specific to the PET scanner provides a means for calculating the percentage of brain tissue emitting radioactive signal at each voxel. The PET count for each voxel was adjusted based on the percent of brain matter.²⁰ Individual PET images were coregistered and aligned in standardized space, intensity normalized to the mean global activity, and smoothed to 16 mm FWHM. Because the anatomy of the aged brain presents spatial normalization problems due to atrophy that distorts topography and makes superposition of identical regions difficult, we used a minimal deformation template (MDT2) derived from a group of aged brains²¹ as the target image. The MDT2 template was created using the T1-weighted images of 25 normal, older individuals with a mean age of 71. A single subject's MRI was selected as a proto-template. This proto-template was then normalized to the 24 other scans using a C-spline warping method.²¹ A deformation field resulted indicating how each voxel in the proto-template deformed to fit each subject. The final deformation field, an average of the 24 deformation fields, was then applied to the proto-template. This resulted in a detailed single-subject scan warped by the average-deformation field of the 24 subjects.

Statistical analyses. Voxel-wise regression analyses were performed on the PET data using statistical parametric mapping software (SPM2, www.fil.ion.ucl.ac.uk/spm/). The main independent variable was FCRP score, with age and diagnostic syndrome (normal, CIND, demented) used as covariates. Voxel-wise glucose metabolic counts, intensity normalized to whole brain activity, were the dependent measure. For exploratory analyses and to support our main FCRP hypothesis, each component of the FCRP score was implemented as the independent variable (regression analyses with age and syndrome as covariates) to investigate their individual metabolic effects. Finally, both age and syndrome alone were regressed with PET to identify their individual effects on metabolism. Regional associations were deemed significant if the *t* statistic reached $p < 0.005$ (uncorrected for multiple comparisons) with a cluster size > 100 .

Table 1 Subject characteristics (n = 58)

Characteristics	CN	CIND	D	Total
Men/women	12/11	15/4	13/3	40/18
Age, y	74.0 (7.0)	75.3 (6.5)	76.7 (8.1)	75.1 (7.1)
Education	15.9 (3.2)	15.3 (2.7)	13.7 (3.2)	14.2 (4.2)
MMSE	29.6 (0.6)*	26.4 (3.6)*	18.9 (6.4)*	25.6 (5.9)
FCRP	8.3 (2.3)	9.7 (2.4)	9.8 (1.9)	9.2 (2.3)

Values are mean (SD).

*Significant difference from all groups, $p < 0.001$.

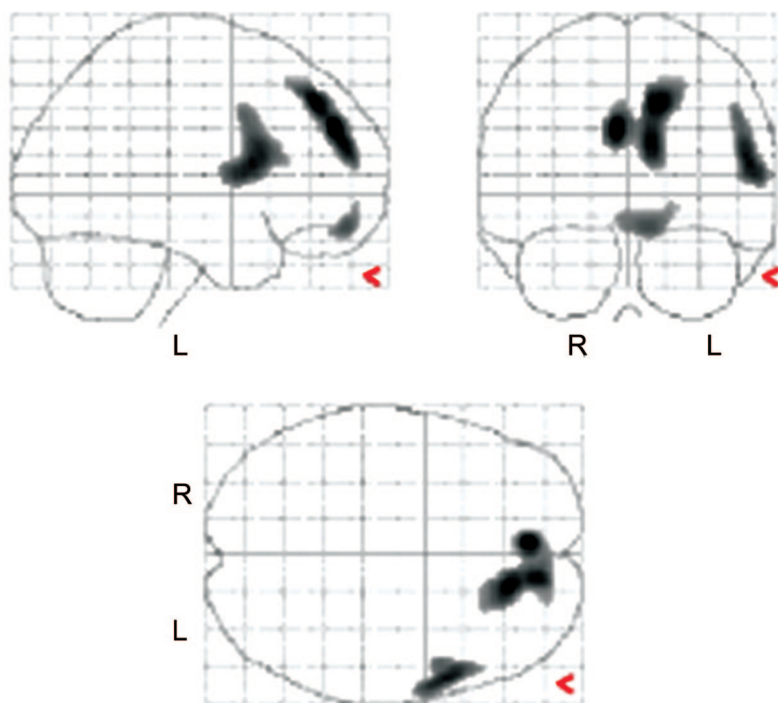
CN = cognitively normal; CIND = cognitively normal not demented; D = dementia; MMSE = Mini-Mental State Examination; FCRP = Framingham Cardiovascular Risk Profile.

RESULTS Subjects were 40 men and 18 women, mean age 75.1 (range 56 to 91), mean years of education 14.2 (range 6 to 22), and mean MMSE 25.7 (range 12 to 30). Twenty-three were CDR = 0 (normal), 19 CDR = 0.5 (questionable impairment), and 16 were CDR = 1 (mild dementia). Table 1 displays the baseline demographics for each group. As a whole, the group was well educated and only moderately cognitively impaired. By classification, those in the demented group had significantly lower baseline MMSE scores compared to the CIND and cognitively normal groups. There were no significant differences between groups regarding FCRP score (median and mode = 9.0 for entire cohort); however, there was a trend for the normal group to be lower than the CIND and dementia groups ($p =$

0.07). There were no significant differences between groups for age or education.

The figure illustrates those significant regions displaying a relationship of higher FCRP correlated with lower metabolism. These regions are the bilateral superior medial frontal, left superior frontal, superior orbital frontal, and ventrolateral prefrontal regions (see table 2 for their corresponding Montreal Neurologic Institute coordinates and associated Brodmann regions). All data are presented in radiologic format.

To further investigate these results, we regressed each component of the FCRP score to reveal individual component effects. Figure e-1 on the *Neurology*[®] Web site at www.neurology.org displays the significant metabolic associations for each component, with the exception of systolic blood pressure due to no significant regional associations. Not surprisingly, many of the individual components reveal associations with regions known to be metabolically affected by AD or CVD (table 3). All individual associations represent a higher value correlating to lower metabolism (history of smoking or diabetes = 1.0, and no smoking or diabetes = 0). Total cholesterol has a striking similarity to the FCRP score results. The similarity between total cholesterol and FCRP prompted a further analysis in which FCRP was regressed with age, syndrome, and total cholesterol as covariates. This analysis reveals the same statistically significant regions (frontal) at a higher threshold ($p < 0.007$), suggesting total cholesterol does contribute to the results seen with FCRP score, but is not the primary factor.

Figure Framingham Cardiovascular Risk Profile (FCRP) inversely associated with metabolism

Results illustrated on SPM glass brain depicting the FCRP score negatively regressed with PET ($p \leq 0.005$, uncorrected; $n = 36$).

DISCUSSION The FCRP, designed to quantify prospective risk of coronary heart disease, is associated with atherosclerosis of the carotid arteries and incorporates several major risk factors for cerebrovascular disease (hypertension, diabetes, age, and smoking). Noteworthy are the individual component analyses. Each component had different metabolic effects and was different from the overall FCRP score associations, with the exception of total cholesterol. Interestingly, there was an association between diagnostic syndrome and the typical characteristic distribution of metabolism in AD, and between age and hippocampal glucose metabolism, but neither of these associations contributed to the association with FCRP. While the individual components show more associations with the temporal and parietal regions, the overall vascular risk (FCRP) was restricted to the frontal lobe. Our data indicate that higher FCRP is correlated with lower glucose metabolism in the frontal lobe. These results persist ($p < 0.007$) when total cholesterol is added as a covariate. Our results

Table 2 Brain regions showing significant correlations			
Correlated brain region (glucose metabolism)	Brodman area	MNI coordinates	Maximum t value
Left frontal inferior opercularis	44, 48	−55, 10, 18	3.39
Left frontal midorbital	11	−7, 54, −13	3.11
Left superior frontal	9	−15, 37, 44	3.48
Bilateral frontal superior medial	9, 32	−8, 45, 33; 7, 48, 31	3.74; 3.63

$p < 0.005$, Cluster size >100 with Framingham Cardiovascular Risk Profile score.
MNI = Montreal Neurologic Institute.

are predominately found in the left hemisphere, which is not uncommon for vascular risk²² or metabolic^{23–25} studies and is obviously dependent on the composition of the cohort and, when relevant, the covariate used in the analysis.

Vascular risk factors are associated with total brain atrophy,^{26,27} and lower brain volumes for pre-frontal regions in older individuals.^{28,29} Further, atrophy has a complicated relationship with metabolism, in which many regions display both atrophy and

lower metabolism but at different degrees.^{30–32} Recently, a voxel-based comparison study revealed that many regions associated with AD displayed a significantly higher degree of hypometabolism than atrophy.³³ Further, we found an association between FCRP and frontal lobe hypometabolism within our cohort using atrophy-corrected data, thus theoretically removing most of the effects related to atrophy. Therefore, the question remains as to why these associations exist.

One explanation is that the FCRP effect is mediated by vascular brain lesions. Perhaps patients with higher FCRP scores have more extensive white matter lesions or more lacunar infarcts, both of which are associated with frontal lobe hypometabolism, and it is these ischemic lesions that actually cause the metabolic change. Cerebrovascular pathology (white matter hyperintensities and subcortical lacunes) is also associated with cortical atrophy^{9,34} that appears to be frontally predominant,²⁹ perhaps due to these pathologic processes being predominate within the frontal

Table 3 Brain regions showing significant correlations ($p < 0.005$, cluster size >100) with the independent factors comprising the Framingham Cardiovascular Risk Profile score			
Correlated brain region (glucose metabolism)	Brodman area	MNI coordinates	Maximum t value
Total cholesterol			
Left frontal superior gyrus	9, 32	−17, 36, 43	3.58
Left superior orbital gyrus	11	−17, 44, −15	3.08
High density lipoprotein			
No gray matter regions			
Diastolic blood pressure			
Right inferior temporal gyrus	20	51, −48, −12	2.98
Left inferior parietal gyrus	40	−35, −52, 44	3.51
Left angular gyrus	7	−35, −57, 44	3.34
Systolic blood pressure			
No significant regions			
History of smoking			
Left hippocampus	20	−29, −16, −19	3.17
Left parahippocampal gyrus	20	−31, −18, −20	3.14
Left fusiform gyrus	20	−36, −5, −33	3.10
History of diabetes			
Bilateral supplementary motor area	6	−4, −16, 63; 4, −16, 63	3.68; 3.44
Bilateral paracentral lobule	4	−3, −27, 64; 3, −27, 64	2.93; 3.01
Left supramarginal gyrus	43	−60, −12, 25	3.71
Left postcentral gyrus	43	−59, −11, 28	3.63
Age			
Bilateral parahippocampal gyrus	20	−35, −20, −25; 29, −20, −24	4.38; 2.99
Bilateral inferior temporal gyrus	20	−43, −9, −35; 40, −12, −31	3.41; 3.08
Left hippocampus	20	−36, −12, −23	3.14
Left fusiform gyrus	20	−43, −12, −29	3.56

MNI = Montreal Neurologic Institute.

lobes, thus primarily affecting this brain region.¹⁵ Simple atrophy is unlikely to explain our findings, however, as the PET data were atrophy corrected. It is possible that our atrophy correction did not fully account for all anatomic (i.e., not metabolic) changes associated with age and disease. However, our results suggest otherwise, as additional areas known to be susceptible to atrophy and anatomic alterations, such as the medial temporal region, were not associated with FCRP in this study. Furthermore, if the FCRP results were due to unaccounted for anatomic alterations, they should appear in the individual component analyses as well, which is not the case. Finally, neuronal dysfunction may precede neuronal death and dropout, and consequently the association of FCRP and frontal metabolism could also be mediated by vascular-based cortical dysfunction, the exact nature of which is unknown.

An alternate explanation is that the effect of FCRP is mediated by AD. Several studies show stroke, hyperinsulinemia, diabetes, current smoking, and hypertension to be associated with AD,^{4,35,36} and AD is also associated with frontal lobe hypometabolism.^{37,38} However, the metabolic signature of AD is hypometabolism in posterior cortex.³⁸⁻⁴⁰ Thus, one would expect that if AD were the culprit, the FCRP score would also correlate with metabolism in inferior parietal lobe and posterior cingulate. This is not the case in our cohort.

In this study we had neither the sample size nor all of the data necessary to convincingly test these alternative explanations of why vascular risk factors correlate with reduced frontal metabolism. This finding, however, provides further evidence of the malignant effects of vascular disease on the brain and expands the known impact to include metabolic alterations affecting prefrontal cortex. technique.

AUTHOR CONTRIBUTIONS

Statistical analyses were completed by Dr. Beth Kuczynski.

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